THE ACTION OF THE GRIGNARD REAGENT ON *CIS-TRANS* ISOMERS

BY

BENJAMIN DIMMICK DEACON

B.A., University of Toronto, 1938

A.M., University of Illinois, 1939

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN
CHEMISTRY IN THE GRADUATE SCHOOL OF
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INTRODUCTION

During the past ten or fifteen years, considerable information has been accumulated concerning the mechanism of organic reactions. One of the factors found to be of considerable importance is the relative space relationships of functional groups involved in reactions. However, an examination of the literature revealed that in only a few cases has the behavior of both the *cis-* and *trans*-forms of a compound toward a series of reagents been studied.

The primary purpose of the present investigation was to prepare both the *cis-* and *trans*-forms of a properly substituted α,β-unsaturated ester, whose structure is such that the two isomers do not readily undergo interconversion. Moreover, the compounds chosen should be such that the steric effects will be easily determined by subsequent reactions such as cyclization.

Specifically this investigation was concerned with the preparation of the *cis-* and *trans*-forms of methyl *o*-benzoxy-cinnamate, and a study of the reactions of each of these isomers with (a) the Grignard reagent, (b) mercuric acetate in methanol, (c) methyl hypobromite, (d) sodium ethoxide, and (e) bromine.

HISTORICAL AND THEORETICAL

Kohler [1] found that both the *cis-* and *trans*-forms of benzaldesoxybenzoin reacted with ethylmagnesium bromide to produce two stereoisomeric ketones, the relative amounts of these being independent of the stereochemical nature of the original α,β-unsaturated ketone. Similarly Colonge [2] found that the ratios of 1,2- to 1,4-addition in the reaction of ethylmagnesium bromide with the *cis-* and *trans*-forms of 3-propyl-3-hexene-2-one and of butylidineacetone were independent of the stereochemical configurations of the starting material.

Johnson [3] obtained some *cis*-2,5-dimethyl-3-hexene-2,5-diol from methyl maleate by the action of methylmagnesium iodide, but methyl fumarate failed to give any diol under the same conditions.

Purdie [4] found that methyl maleate reacted with phenylmagnesium bromide to form 2,2,5,5-tetraphenyl-2,5-dihydrofuran, while methyl fumarate, under the same conditions, produced only an uncrystallizable syrup.

Wright [5] has found that the *cis*- and *trans*-forms of methyl cinnamate react with mercuric acetate in methanol, each isomer producing its own characteristic stereoisomer of methyl α-acetoxymercuri-β-methoxy-hydrocinnamate.

Carter [6] added methyl hypobromite to the *cis*- and *trans*-forms of cinnamic acid to produce the stereoisomeric α-bromo-β-methoxy-hydrocinnamic acids.

Purdie [7] treated ethyl cinnamate with sodium methoxide in methanol, and found that methyl cinnamate had been formed. Similarly Bishop [8] found that phenyl benzoate reacted with sodium ethoxide in ethanol to form ethyl benzoate and sodium phenoxide.

Reimer and Howard [9] carried out the bromination of the *cis*- and *trans*-forms of *o*-methoxy-cinnamic acid. A mixture of the two stereoisomeric dibromides was obtained, the lower-melting form being produced in higher yield from the *cis*-acid than from the *trans*-acid.

DISCUSSION OF RESULTS

The *cis*- and *trans*-forms of methyl *o*-benzoxy-cinnamate [10] were treated with phenylmagnesium bromide. From both forms, 2,4-diphenyl-2-chromanol was isolated, and identified by dehydration to 2,4-diphenyl-1,4-benzopyran.[11] The yield of this product was found to be higher from the *trans*-isomer than from the *cis*-isomer. Triphenylcarbinol was also obtained, as expected, from both isomers. When the remaining oily material produced from the *trans*-isomer was subjected to vacuum distillation, some 4-phenylhydrocoumarin was obtained, but none was obtained from the *cis*-isomer.

Mercuric acetate in boiling methanol reacted with methyl *o*-benzoxy-*cis*-cinnamate to form a methoxy-triacetoxymercuri compound, whereas the *trans*-isomer produced a methoxy- diacetoxymercuri derivative. Attempts to brominate these mercurials were unsuccessful.

Methyl hypobromite reacted with both the *cis*- and *trans*-forms of methyl *o*-benzoxy-cinnamate to produce the two racemic forms of methyl *o*-benzoxy-α-bromo-β-methoxy-hydrocinnamate. The product from the *trans*-isomer melted at 95-96° and the other isomer at 119-120.5°. Hydrolysis of both of these isomers produced coumarilic acid in low yield.

Methyl hypobromite was found to react with methyl *o*-hydroxy-*trans*-cinnamate to produce methyl 3,5,α-tribromo-β-methoxy-melilotate. Alkaline hydrolysis of this product yielded 5,7-dibromocoumarilic acid.

Sodium ethoxide in ethanol was found to react with methyl *o*-benzoxy-*cis*-cinnamate to produce coumarin. When the reaction was carried out in the same manner with the *trans*-isomer, it was recovered unchanged.

The *trans*-form of methyl *o*-benzoxy-cinnamate reacted with bromine in acetic acid to produce a dibromo compound which melted at 94-95° when purified. Under the same conditions the *cis*-isomer gave an oil which refused to crystallize, and when brominated in chloroform a small amount of the same dibromo compound, which had been obtained from the *trans*-isomer, resulted.

SUMMARY

The *cis*- and *trans*-forms of methyl *o*-benzoxy-cinnamate have been prepared and their reactions with a series of reagents investigated.

Phenylmagnesium bromide reacted with both forms to produce the same 2,4-diphenyl-2-chromanol. From the *trans*-form some 4-phenylhydrocoumarin was obtained, but none was obtained from the *cis*-isomer.

Mercuric acetate in methanol combined with the *cis*-isomer to give a triacetoxymercuri compound, while the *trans*-isomer produced a diacetoxymercuri derivative.

Methyl hypobromite added to both isomers to give isomeric products which were the two racemic forms of methyl *o*-benzoxy-α-bromo-β-methoxy-hydrocinnamate. Both of these isomers cyclized on boiling with dilute alkali to produce coumarilic acid in low yield.

The *cis*-isomer reacted with sodium ethoxide in boiling ethanol to produce coumarin, whereas the *trans*-isomer, when treated in the same way was recovered unchanged.

The *trans*-isomer reacted with bromine in acetic acid to produce a dibromo compound, whereas the *cis*-form under the same conditions produced an oil which refused to crystallize. The *cis*-isomer reacted with bromine in chloroform to give a low yield of the same dibromo compound as produced from the *trans*-isomer.

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ADDENDUM

AN ATTEMPTED RESOLUTION OF TRÖGER'S BASE

HISTORICAL AND THEORETICAL

Tröger[1] prepared a compound from the condensation of *p*-toluidine and formaldehyde in acid solution. The work of Spielman[2] and of Wagner[3] has shown that the structure of the compound is 1,2′-methylene-3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline. A study of a model of this showed that no elements of symmetry are present due to the presence of two asymmetric tertiary nitrogen atoms. From the model it was seen that the molecule should be folded on the N-CH_2-N axis, and hence rigidity should therefore be imparted to the molecule. It was therefore desirable to attempt its resolution.

DISCUSSION OF RESULTS

Attempts to resolve this base by means of *d*-tartaric acid were unsuccessful since it was found that the base is apparently too weak to form salts with this acid. Salts were isolated by use of *d*-camphor-10-sulfonic acid and with *d*-*a*-bromo-π-camphorsulfonic acid. However, fractional crystallizations of these salts failed to give fractions of different rotations, and decomposition of the salts with ammonium hydroxide produced only the inactive base.

SUMMARY

Tröger's base formed salts with *d*-*a*-bromo-π-camphorsulfonic acid and with *d*-camphor-10-sulfonic acid, but these salts failed to give diastereoisomers on fractional crystallization. Decompositions of the fractions obtained yielded only the inactive base. Thus, these acids were found to be ineffective as resolving agents for Tröger's base.

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VITA

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